REMARKS

The fees for a two month extension of time and for the accompanying Notice of Appeal should be charged to Deposit Account No. 02-1818. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 02-1818. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 02-1818.

Claims 1-2, 6, 9, 12, 14, 16, 18 and 21-26 are pending. Claims 3-5, 13, 15 and 27-31 are withdrawn from consideration as drawn to non-elected species. Claims 1, 2, 6, 9, 12, 14, 16, 18 and 21-23 have been examined on the merits in this application. Claims 6, 14, 16, 21 and 23 are deemed allowable. Claims 1, 6, 14, 16 and 21 are amended and claims 24-31, which are dependent on allowable claim 23 are added. Claims 6, 14, 16 and 21, which are deemed allowable, but are dependent upon a rejected base claim are rewritten as independent claims incorporating all limitations. Thus claims 6, 14, 16, 21, 23 and claims dependent thereon should be allowable.

In addition, Claim 1 is amended to render it clear that the imaging/detecting step of the method as claimed is practiced on a live subject, that the internal wounds/inflamed tissues are imaged, and that the an element of the method is selecting a subject to be tested for internal wounds or inflamed tissue, not selecting a subject to use as a model for studying bacterial trafficking. The claims thus render it clear that the claimed method is for detecting internal inflamed or wounded tissues in a subject. The subject is selected because he/she is suspected of having internal inflamed or wounded tissue (or does not). The subject is imaged to detect the internal wounded/inflamed tissue. The claims are not directed to a method for studying bacterial trafficking by administering bacteria, using a rodent model, not a subject suspected of having internal or wounded tissue, but a subject who is to be externally burned, and determining where the bacteria traffic by excising organs. Claim 23, which has been deemed allowable, is rewritten as an independent claim, incorporating all limitations of base claim 1 prior to the amendment herein.

Claims 3-5, 13 and 15, which are directed to non-elected species, are withdrawn. They are retained pending allowance of a generic claim. Applicant reserves the right to file continuing/divisional applications to non-elected, cancelled and unclaimed subject matter.

THE REJECTION OF CLAIMS 1, 2, 9, 12, 18 AND 22 UNDER 35 U.S.C. §102(b)

Claims 1, 2, 9, 12, 18 and 22 are rejected under 35 USC §102(b) as anticipated by Fu *et al.* because Fu *et al.* allegedly discloses a method for detecting wounded or inflamed tissue

inside of a subject, comprising systemically administering to a subject a detectable, non-pathogenic bacterium that replicates in the subject, is recognized by the immune system of the subject and is not targeted; and monitoring the subject to detect the accumulation of the bacterium at or in a wounded tissue or inflamed tissue inside of the subject. The Examiner stated in the previous Office Action that the *E. coli* was recognized and cleared by the immune system, and thus is considered nonpathogenic, and uses the pUC19 plasmid, which encodes the antibiotic ampicillin as a therapeutic agent. The Examiner alleges that because "living bacteria were found to have reached the burn tissue after traveling through the stomach, lining of the gut, and the liver, they replicate in the subject." The Examiner continues and states that because ampicillin was expressed, the *E. coli* are considered to comprise an inducible promoter regulating expression of ampicillin, that is, expression of ampicillin from the pUC19 vector is inducible upon introduction of the vector into a bacterial cell. Other comments of the Examiner are discussed in turn below. This rejection respectfully is traversed.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the 'prior art' . . . the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be

entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). *In re Arkey, Eardly, and Long*, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

Rejected claims

Claim 1, and all claims dependent thereon recite:

Claim 1 recites:

> A method for diagnosis by imaging wounded or inflamed tissue inside of a live subject, comprising:
>
> identifying a subject suspected of having an internal wound or inflammation to be tested for the presence or absence of internal wounded tissue or internal inflamed tissue;
>
> systemically administering to the subject in whom the presence or absence of a wounded tissue or inflamed tissue is to be detected, a bacterium, wherein:
>
> the bacterium encodes a protein that is detectable by imaging in the subject or encodes a protein that induces a signal detectable by imaging;
>
> the bacterium replicates in the subject;
>
> the bacterium is not pathogenic to the subject and is recognized by the immune system of the subject;
>
> the bacterium is not targeted; and
>
> after a sufficient time for the bacterium to accumulate in wounded or inflamed tissues inside of the subject, imaging the detectable bacterium inside of the live subject to detect accumulation of the bacterium in the subject, and thereby imaging wounded or inflamed tissues inside of the live subject, wherein imaging the accumulation indicates the location of wounded tissue or inflamed tissue inside of the subject.

Dependent claims recite particulars of the method. For example, Claim 2 is dependent on claim 1 and recites that the bacterium encodes a protein(s) for the therapy of the detected wounded or inflamed tissue. Other dependent claims specify therapeutic proteins, detectable proteins or proteins that induce a detectable signal and detection methods.

As discussed previously and below, Fu *et al.*, discloses detecting bacteria in excised tissue, not imaging wounded or inflamed tissue inside of a subject. Fu *et al.* discloses administering fluorescently labeled bacteria into Wistar rats through a gastric catheter, and **then** inducing third degree burns on the **outside** of the animal (not internally) in order to study trafficking of intestinal bacteria. After predetermined time periods, the rats were **sacrificed** and organs and subeschar tissue **excised** to assess bacterial infection, **not to detect** wounded or inflamed tissue (nor is there evidence that the excised organs contained wounds or inflamed tissue) by fluorescence. Therefore, Fu *et al.* discloses administering bacteria,

burning the skin (externally) of the animal; sacrificing it, detecting bacteria in excised tissue from a dead animal in order to study trafficking of intestinal bacteria to severe burns on the skin.

Disclosure of Fu *et al.* and differences from the instant claims

Fu *et al.* is directed to a study of the role of bacteria in the gut in severe burn infections. **Fu *et al.* does not disclose any method for diagnosis of internal wounds nor internal inflamed tissues nor any step of detecting/imaging internal wounded/ inflamed tissues nor doing so in a live animal.** Fu *et al.* detects bacteria in excised tissue in order to study trafficking of intestinal bacteria to severe burns on the skin. The excised tissue is not identified as wounded or inflamed nor is it described as wounded or inflamed. Fu *et al.* does not perform imaging. Fu *et al.* concludes that intestinal bacteria can traffic through damaged intestinal wall and cause infections of burns on the skin.

In particular, Fu *et al.* provides a study assessing the role that fecal organisms play in burn wound infection. To study this role, Fu *et al.* provides an animal model to observe the:

> dynamics of fecal organisms and burn wound organisms in attempts to investigate the relationship between translocation infection by fecal organisms and burn wound infection more precisely.

Thus, Fu *et al.* does not disclose or even hint at a method for detecting wounds or inflamed tissues internally in a subject. The burn wounds are external burns.

To assess the role of fecal organism translocation in infecting burn wound, fluorescently labeled bacteria were introduced into Wistar rats through a gastric catheter, **followed by third degree burning of skin of the rats**. Thus, the bacteria **are not introduced into** a subject suspected of having internal wounded or inflamed tissue and in whom, while alive, the wounded/inflamed tissue is to de detected, but into a subject who is to be **burned,** sacrificed, and the path of fecal bacteria determined.

After predetermined time periods, following administration of bacteria and then burning the rats to produce external wounds, the rats were sacrificed and organs excised to detect bacteria, not inflammation or wounding by fluorescence. Thus, Fu *et al.* does not disclose imaging accumulation of bacteria in wounded or inflamed tissue in a live subject, but rather sacrifices the subject and excises the organs to detect bacteria, not to determine if the excised organs are wounded or inflamed. Clearly, this is not a diagnostic method; sacrificing the subject renders any diagnosis moot.

In another group of rats, bacteria containing pUC19 to provide ampicillin resistance for selection (not therapy) were inoculated into the intestines of the rats through a catheter,

and fed ampicillin to select for the introduced bacteria. After confirming that the Amp-resistant bacteria were incorporated into the intestinal tract, the rats were burned, and then sacrificed and their organs harvested and bacteria cultured in medium containing ampicillin. Plasmid was extracted and identified by restriction digestion patterns. This is not imaging nor is it detection of wounded and inflamed tissue. The plasmids reflect trafficking of the bacteria, not accumulation in wounds.

Fu *et al.* states that the results indicate that in the early stage of a severe burn, intestinal bacteria can penetrate through the intestinal membranous barrier and disperse. Thus, enterogenous infection should be considered in cases of sepsis in early burn stages. Fu *et al.*, thus, discloses that intestinal flora can cause sepsis in severe burns on the skin. Fu *et al.* provides an animal model for studying such infections, and does not perform any imaging and does not detect wounds or inflamed tissues or even the accumulation of bacteria in a live animal in internal wounds or inflamed tissue as required by the instant claims. Fu *et al.* does not disclose a method for detection of wounded and inflamed tissues inside a subject (the animal is dead, there is no reason to detect such tissues); Fu *et al.* is studying infection following severe burns; no detection of internal wounds and inflamed tissue is involved. Fu *et al.* does not disclose systemically administering detectable bacteria to a subject, and then detecting accumulation of the bacteria in order to identify the location of an internal wound or inflamed tissue in a live subject. While Fu *et al.* uses detectable bacteria, the method is for detecting bacteria, by administering bacteria and externally burning a subject to see where the bacteria traffic in the subject. The detected and excised organs are not wounded or inflamed. This is not a method for detecting wounded or inflamed tissue in a subject by administering bacteria.

As discussed, the claims are directed to methods of imaging internal wounded or inflamed tissue by administering bacteria to a subject suspected of having such internal wounded or inflamed tissue, then imaging the **live** subject to detect the internal wounded or inflamed tissues. Thus, the claims clearly recite a method that differs from the study described in Fu *et al.* Such differences, as noted above, include administering bacteria to an animal, then wounding it externally, then sacrificing it, and then excising organs to detect the bacteria. No wounds or inflamed tissues (internal or external) are imaged or even detected; and no live animal is imaged. Fu *et al.*, thus, does not disclose all elements of claim 1 nor any claim. Therefore, Fu *et al.* does not anticipate any pending claim.

Rebuttal to comments of the Examiner:

1) The Examiner states that: Fu *et al.* clearly detected the administered bacteria in burn wounds. That Fu *et al.* may have been studying bacterial trafficking is irrelevant, this is not a 35 USC 103 rejection. It is not irrelevant because Fu *et al.*, does not include a step of detecting internal wounded or inflamed tissue. Applicant has argued and is arguing, not that Fu *et al.* does not suggest the method (which it does not), but that Fu *et al.* does not disclose the method as claimed. Fu *et al.* does not disclose imaging (or detecting) internal wounded or internal inflamed tissue in a subject. A burn on the skin is not inside a subject; skin is not inside the subject, no matter how deep the wound.

2) The Examiner states that: Fu *et al.* detects bacteria that accumulate in a burn on the outside of a subject. Fu *et al.* does not image (or detect) internal wounds or internal inflamed tissue. Skin is on the outside of a subject (there would be no conceivable reason (nor does the claim encompass) practicing a method to administer bacteria to detect a wound on the outside of a subject (particularly one inflicted by the user of the method); wounds and inflamed tissues, such as in atherosclerotic plaques, inside of a subject cannot be directly detected). Thus, the claim cannot be anticipated by Fu *et al.* In addition, Fu *et al.* looks for the bacteria on sacrificed animals; clearly this is not a method for detecting wounded or inflamed tissue.

3) The Examiner states that: Applicants present no reasoning or logic as to why a burn is not to be considered "a wounded or inflamed tissue." Applicant respectfully submits that a burn is indeed a wound, but a burn on the skin of an animal is not an internal wound, which is detected by the instantly claimed methods. As noted above, Fu *et al.* is not detecting wounded or inflamed tissue, and clearly not internal wounded or inflamed tissue. The excised organs are not wounded or inflamed, they are excised as part of the detection of the trafficking of the bacteria; there is no disclosure in Fu *et al.* that the organs were wounded or inflamed. The burns on the outside of the animal were visible; bacteria were not detected to detect wounded or inflamed tissue, but to detect the path of the bacteria. Thus, Fu *et al.* is **not** detecting wounds or inflamed tissue (external or internal), but is detecting bacteria.

4) The Examiner urges that: Fu *et al.* teaches "all the instant claim limitations, even though the purpose of Fu *et al.* may have differed from the instant claims."

As discussed above, this is not correct. Fu *et al.* does not detect internal wounds or inflamed tissues; the burns are external burns. All steps in Fu *et al.* are designed to detect

bacteria. The instant claims (as amended or previously pending) do not recite a method that encompasses administering bacteria and then wounding a subject. Claims are to be read in light of the specification (and also include the knowledge of one of ordinary skill in the art). There is no method of diagnosis in which a reagent to detect a condition is administered and then the condition is induced. Such is not a method of detection or diagnosis.

Further, as noted, the claims recite that the method is for detection/imaging of inflamed or wounded tissue inside of a subject. This is affirmatively part of the method; Fu *et al.* neither detects inflamed or wounded tissue (it detects bacteria and the bacteria are on the outside of the subject). Furthermore, the method of Fu *et al.*, is not a method of diagnosis of any sort (another affirmative requirement of the instant claims); the animals are dead. As amended, the claims explicitly recite, what previously was implicit: the method is practiced on live subjects.

5) The Examiner urges that: a reading of the claims reveals that there is no set limitation as to when the wounded or inflamed tissue must be present relative to the administration of the bacteria. The Examiner states that the:

> claims recite "a subject to be tested", which implies wounds in the present or perhaps in the future.

The rejected claims are amended to recite that the subject is suspected of having internal wounded or inflamed tissues; thereby rendering it clear that the wounds are not inflicted after administration of the bacteria.

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In view of the above, reconsideration and allowance of the application respectfully are requested.

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 3800002.00055 / 4804US
Address all correspondence to:
Stephanie Seidman
K&L Gates LLP
3580 Carmel Mountain Road, Suite 200
San Diego, California 92130
Telephone: (858) 509-7410
Facsimile: (858) 509-7460
email: stephanie.seidman@klgates.com